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**Title:**

A Rare Presentation of Hypercalcemia in a Patient with Urothelial Adenocarcinoma

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## **Abstract**

**Introduction:** Hypercalcemia is rare in urothelial cell carcinoma. When it does occur it typically is through a PTHrP-mediated process.

**Material and Methods:** A 58-year-old male presented with mental confusion, unsteady gait, and bladder distension due to hypercalcemia. Imaging showed recurrent urothelial adenocarcinoma confirmed by tissue biopsy and immunohistochemical staining.

**Result and Discussion:** The etiology of this patient's hypercalcemia was unclear as it did not fit the typical pattern of paraneoplastic hypercalcemia. The patient had good response to supportive therapy but he continued to have acute episodes of hypercalcemia until his demise 5 months later.

**Conclusion:** Paraneoplastic hypercalcemia in urothelial adenocarcinoma is typically a PTHrP-mediated process although this case did not have a definitive etiology. It is important to be aware of this presentation and to suspect in a patient with supporting clinical symptoms.

## **Introduction**

Paraneoplastic hypercalcemia is a common syndrome and is estimated to occur in up to 20-30% of cancer patients [1, 2]. The development of hypercalcemia portends a poor prognosis as it is generally associated with advanced disease with only 30 day median survival after the first episode [3, 4]. The most common cancers associated with hypercalcemia are lung, renal cell, breast, and multiple myeloma [5]. Currently the understood mechanisms for paraneoplastic

hypercalcemia are PTHrP-related hypercalcemia (80%), osteolytic hypercalcemia (20%), excess extrarenal vitamin D (<1%) and ectopic hyperparathyroidism (<1%) [2].

Paraneoplastic hypercalcemia associated with urothelial carcinoma is rare. One observational study of urogenital malignancies found only 6 instances of hypercalcemia out of 321 cases of bladder cancer (1.9% incidence) [6]. The major causes of paraneoplastic hypercalcemia in urothelial carcinoma is by overproduction of PTHrP [7-10] or more rarely osteolytic bone metastases [11]. We report an unusual case of hypercalcemia by unknown mechanism in a patient with relapsed urothelial carcinoma.

## Case Report

This patient is a 58-year-old male with a history of urothelial cell carcinoma invading into muscle, Stage 3 (pT3N0) treated with neoadjuvant chemotherapy with cisplatin and gemcitabine. He then underwent radical cystectomy followed by urinary diversion via creation of a neobladder. He was doing well until 13 months later when he presented to the Emergency Department for bladder distension, difficulty self-catheterizing, mental confusion, and unsteady gait. The initial laboratory results show an unexpected elevation of calcium to 16.0 mg/dL (8-10.4 mg/dL), with repeat ionized calcium 9.6 mg/dL (4.5-5.6 mg/dL). Electrocardiogram (EKG) showed tachycardia with shortened QT interval (291ms). On review of symptoms he endorsed unintentional weight loss of 7 kilograms, night sweats, and generalized weakness.

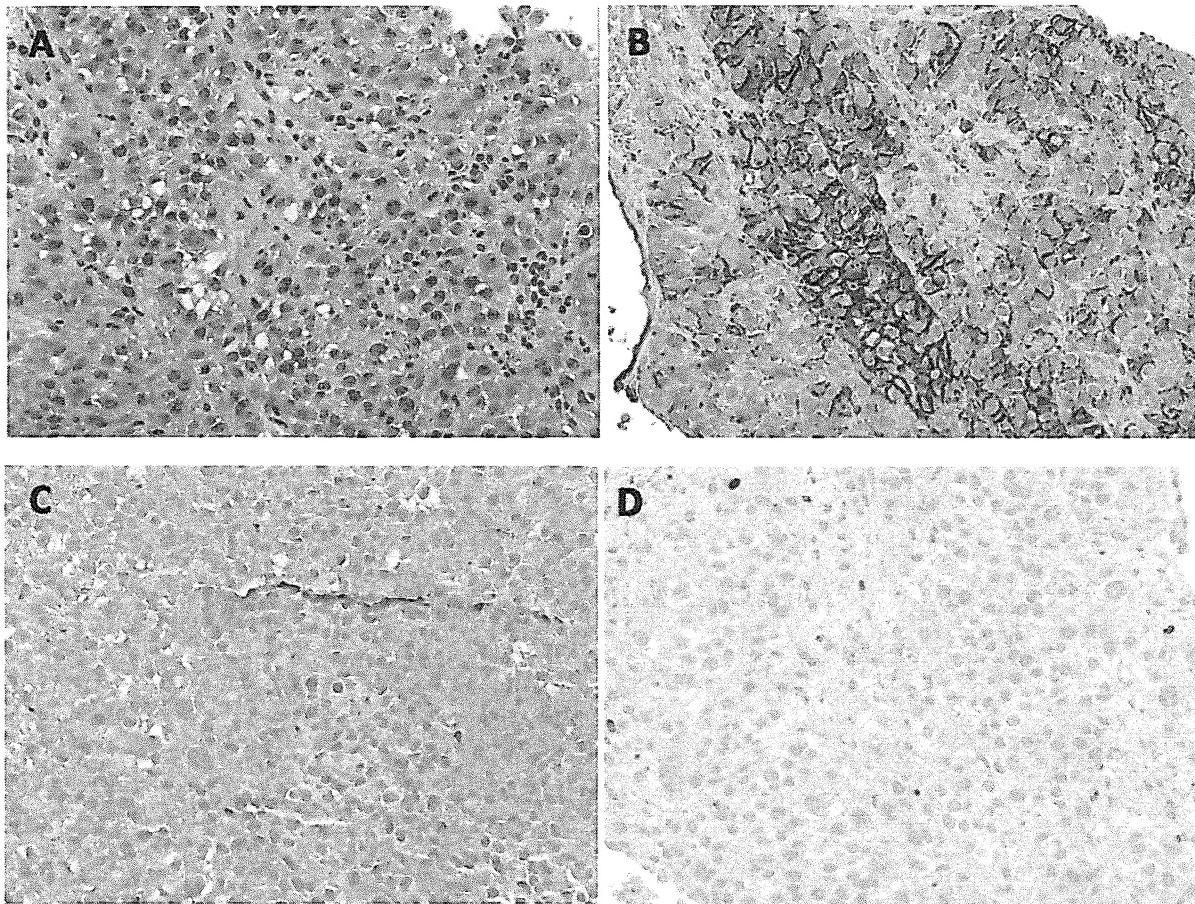
The patient was admitted and further workup showed parathyroid hormone (PTH) 6.0 pg/mL (15-65 pg/mL), PTHrP 1.8 pmol/L (<2.0 pmol/L), 1,25-dihydroxyvitamin D 81.5 pg/dL (19.9-79.3 pg/dL), serum and urine protein electrophoresis did not reveal M protein, and angiotensin converting enzyme (ACE) 31 U/L (14-82 U/L). Computer tomography (CT)

urogram demonstrated a new 11 x 7 x 10 cm heterogeneous enhancing mass with indistinct margins in the pelvis consistent with recurrent bladder cancer (Figure 1).



**Figure 1. CT Urogram demonstrates a large heterogeneous mass in the pelvis measuring 11cm x 7.1cm x 10cm with indistinct borders and mass effect against the rectum**

CT chest/abdomen/pelvis showed interval increase in size of a right upper lobe pulmonary nodule (7 mm) and new 1.2 cm lesion in the left hepatic lobe concerning for metastatic progression. A bone scan did not reveal any acute bony lesions. Biopsy of the pelvic mass and pulmonary nodule revealed poorly differentiated carcinoma with squamous features which was morphologically similar to his initial biopsy. Immunohistochemical profiles supported morphologic findings with positive staining for thrombomodulin, Lu-5 and p63 from the pelvic tissue and positive thrombomodulin and P40 in the lung tissue favoring urothelial origin (Figure 2). Both lung and pelvic tissues were negative for GATA-3 and uroplakin which is unusual but can be negative in up to 33% of cases and usually portends a more aggressive tumor.



**Figure 2. Biopsy of pelvic mass showed:** A) Epithelioid malignant cells with enlarged nuclei, prominent nucleoli, moderate to abundant cytoplasm, and squamous differentiation (H&E 20XB.) Tissue immunohistochemical staining was positive for thrombomodulin (B), negative for uroplakin (C), and negative for GATA 3 (D) consistent with patient's prior urothelial cell carcinoma

The patient's hypercalcemia was treated supportively with intravenous fluids, calcitonin 300 IU/ml units and zoledronic acid 4mg with improvement of serum calcium to 9.5 mg/dL (8-10.4 mg/dL). He was started on palliative radiation therapy and immunotherapy with atezolizumab, a monoclonal antibody against programmed cell death-ligand 1 (PD-L1). Unfortunately the patient experienced two additional episodes of acute hypercalcemia prompting inpatient admission for supportive therapy. Five months after diagnosis he passed away at home on hospice care.

## **Discussion**

This patient's presentation was most consistent with paraneoplastic process as his hypercalcemia did not occur until he had a relapse of his urothelial carcinoma. However the exact mechanism underlying this patient's hypercalcemia could not be elucidated. The most common etiologies for hypercalcemia of malignancy are overproduction of PTHrP or bone destruction from osteolytic metastases. In this case, the patient had a low level of PTHrP 1.8 pmol/L (repeat was 1.6 pmol/L) which does not support PTHrP-mediated hypercalcemia. Furthermore, this patient had no evidence of bony metastases on bone scan that could explain his hypercalcemia. The patient also had decreased levels of PTH suggesting normal physiologic suppression as well as normal levels of 1,25-dihydroxyvitamin D. The workup for other unusual causes for hypercalcemia such as sarcoidosis also was negative.

Hypercalcemia is a rare sequela of urothelial carcinoma. In reported literature, the most common mechanism of hypercalcemia in urothelial carcinoma is due to overproduction of PTHrP [7-10] . One hypothesis for this patient's hypercalcemia is that the tumor was producing PTHrP that could not be measured in the plasma but still caused a physiologic response. In a case of relapsed transitional cell carcinoma with PTHrP mediated hypercalcemia reported by Matsuoko et al., PTHrP was detected in the serum and in the tumor tissue by immunohistochemical studies. It is possible that this patient's tumor tissue could have been expressing PTHrP, though it was never formally tested as it is not a standard diagnostic test for hypercalcemia.

Another hypothesis for this patient's hypercalcemia is that his malignancy was producing another molecule that induced hypercalcemia that current laboratory technology is unable to

measure. PTHrP was not able to be quantitatively measured until 1987, but the idea of a parathyroid hormone like molecule was surmised as early as the 1940s [12]. Currently PTHrP is thought to induce hypercalcemia by binding to PTH receptors in the tissues as well as playing a role as a local factor in the bone environment by regulating endochondral bone development. It is feasible that this patient's tumor cells produced a molecule that mimics PTHrP structurally or functionally but has not yet been identified.

Izard et al. has reported cases of paraneoplastic leukocytosis associated with urothelial carcinoma, with two thirds found to have concurrent hypercalcemia. Interestingly, two months after diagnosis of recurrent metastatic disease our patient began to have a persistent leukocytosis that peaked at  $95 \times 10^3$  ( $3.4-9.8 \times 10^3$ ). He was tested repeatedly for an infectious cause and was treated with broad spectrum antibiotics for bacteremia and complicated urinary tract infections. Despite antibiotic therapy and blood and urine culture clearance he continued to have a rapid rise in WBC over the next 3 months. It is unknown if there is a correlation between hypercalcemia and paraneoplastic leukocytosis but both are associated with a very poor prognosis

## Conclusion

This case illustrates a unique presentation of recurrent metastatic urothelial carcinoma presenting with hypercalcemia. Despite exhaustive laboratory and radiologic workup, we were unable to show a definite etiology of his hypercalcemia. The most likely cause of hypercalcemia in this patient is a paraneoplastic process mediated by PTHrP-like molecule given the strong association of PTHrP mediated hypercalcemia with squamous cell neoplasms. The identity and nature of this molecule remains to be elucidated. Although hypercalcemia is rarely associated

with urothelial cell carcinoma, it is important to be aware of this presentation and to have a high index of suspicion in a patient with clinical symptoms.

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